Journal of Acute Disease

journal homepage: www.jadweb.org

doi: 10.4103/2221-6189.221288

Latest research progress on acute nephrotic syndrome

Satinder Kakar✉, Vishal Kumar, Ramandeep Singh

Department of Pharmacy, Himachal Institute of Pharmacy, Paonta Sahib (H.P), India

ARTICLE INFO

Article history:
Received 15 September 2017
Revision 20 September 2017
Accepted 8 October 2017
Available online 1 November 2017

Keywords:
Nephrotic
Child
Protein

ABSTRACT

Etiology of nephrotic syndrome is somewhat complex in nature. It may range from primary to secondary forms. Nephrotic syndrome patients often need immunosuppressive treatment although it has some side effects and may lead to renal disease which may be acute or severe. This review deals with herbal treatment and other recent approaches for treating symptoms of nephrotic syndrome.

1. Introduction

Nephrotic syndrome (NS) is an acute renal disorder in pediatric population. It may occur in adult population also, but pediatric population is most affected. NS is having high amount of the protein in urine and low serum albumin, abundant albuminuria, generalized edema, and hyperlipidemia[1]. It occurs worldwide and captures at any age, but it generally occurs in initial years of life, more around 4-5 years and is more prevalent in spring season[2,3]. No specific cause has been identified yet although there are many etiologic factors for it, and the renal pathology varies for different cases, but most seen in childhood cases, in temperate climates, and renal histology by light microscopy is unworthy and of little use. These cases are known as 'minimal change' NS and represents vast majority of patients. 'Minimal change' NS or idiopathic NS covers vast literature on NS in childhood. Diseases restricted to a particular place such as nutritional oedema and urinary schistosomiasis may simulate, distort, or uncertain renal pathology, and conditions of practice make impossible the use of radiologic, immunologic investigations *etc*., required to identify and characterize renal disorders, thus clinical recognition of renal disease is rendered difficult[4,5].

2. Types

2.1. Minimal change disease (MCD)

1) Characterised as childhood NS, prevalent in 77%-85% of cases.

2) Idiopathic in nature, some reports in adult cases showed an association with Hodgkin lymphoma.

3) Renal biopsy samples when subjected to light microscopy showed no change.

4) On electron microscopy, tissue thinning can be seen.

5) Staining via florescence for immune complexes was negative.

2.2. Focal segmental glomerulosclerosis

1) Prevalent in 10%-15% of cases.

✉First and correspondence author: Satinder Kakar, Department of Pharmacy, Himachal Institute of Pharmacy, Paonta Sahib (H.P), India.
E-mail : satinder.kakkar5@gmail.com

How to cite this article: Satinder Kakar, Vishal Kumar, Ramandeep Singh. Latest research progress on acute nephrotic syndrome. J Acute Dis 2017; 6(6): 255-259.

2) Characterised as adulthood NS.

3) Light microscopy of renal biopsy sample showed sclerosis in portions of selected glomeruli, which can progress into global glomerular sclerosis.

4) Tissue thinning was seen on electron microscopy, which was negative in most cases[6].

3. Classification

NS is categorised as primary, secondary and miscellaneous ones. Primary form includes minimal change nephritic syndrome, focal segmental glomerulosclerosis and membranous nephropathy. Secondary forms includes infections-hepatitis B and C, human immunodeficiency virus, malaria, toxoplasmosis, as well as syphills. Miscellaneous forms includes systemic lupus erythematosus, immuoglobulin A nephropathy and diabetes mellitus. Drugs used are gold, non-steroidal antiinflammatory drugs, pamidronate, interferon, heroin and lithium.

4. Pathophysiology

NS with inherited causes involves autosomal recessive type, NS type Ⅰ, NS type Ⅱ and isolated diffuse mesangial sclerosis[7]. Glomerular filtration barrier has three layers that is fenestrated endothelium, glomerular basement membrane, visceral glomerular epithelium containing podocytes (Figure 1). In NS, disturbance of the normal filtration process of glomerulus occurs, thus protein passage through filtration barrier due to three reasons including glomerular basement membrane's defects, T-cells in the damage to podocytes leading to MCD of NS, and pathology changes according to the type of NS[8,9] (Figure 2). Also, there were some researches carried out on NS (Table 1).

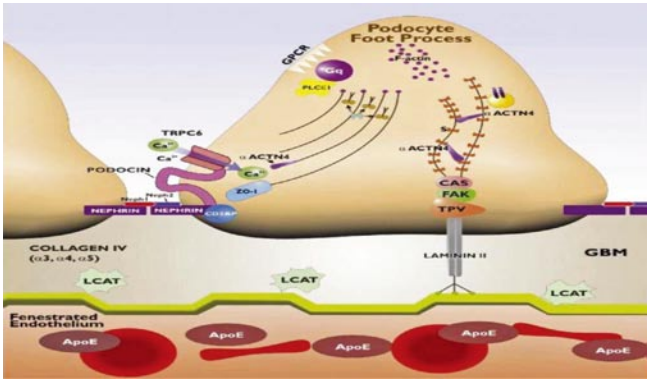

Figure 1. Pathophysiology of NS.

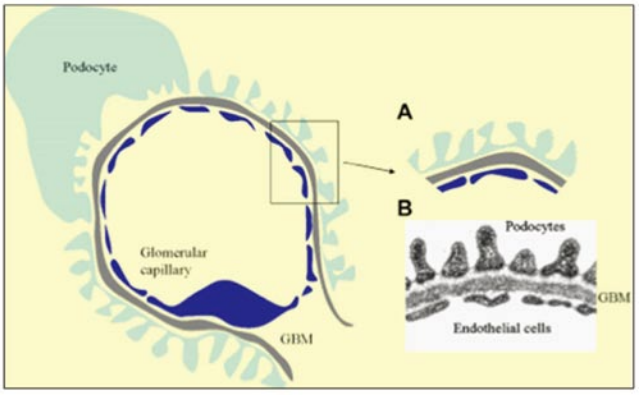

Figure 2. Glomerular filtration barrier.

5. NS in people of different age

NS is an acute disease, and is a MCD. T lymphocyte dysregulation and vascular factors affecting permeability that

Table 1

Researches on NS.

Scientists	Researches
Haas *et al*[10]	Role of proprotein convertase subtilisin/kexin type 9 in NS
Singhal and Brimble[11]	Thromboembolic complications in the NS
Caridi *et al*[12]	Podocin mutations in NS reported
Moulin *et al*[13]; Lewis *et al*[14]; Hinkes *et al*[15]	Cloning uncovers mutations in phospholipase C epsilon 1
Vernier *et al*[16]; Joven *et al*[17]; McCarthy *et al*[18]	Sequencing of 24 genes associated with steroid-resistant NS
Drewe *et al*[19]	Treatment with etanercept in patients with the tumor necrosis factor receptor was reported

Table 2

Reported incidence of NS associated with thromboembolism.

Researches	Number	TE	Study type	Notes
Childhood				
Lilova *et al*[26]	447	9(2.0%)	Retrospective	Only symptomaticTE reported
Hamed *et al*[27]	30	4(13.0%)	Retrospective	Only congenital nephrotic syndrome
Kerlin *et al*[28]	326	30(9.2%)	Retrospective	Only symptomatic TE reported; included secondary causes of NS
Adults				
Cherng *et al*[29]	89	29(32.6%)	Prospective	VzQ evidence of PE
Wysokinski *et al*[30]	218	44(20.2%)	Retrospective	RVT and DVT

may change podocyte function and permselectivity are marked as important features according to the research studies. Podocyte proteins coded mutations in genes have also been identified. NS patients has high risk for infections and thromboembolic episodes. Persistent hyperlipidaemia and prolonged steroid therapy comes into play.

In variable population of patients, treatments with levamisole, cyclophosphamide and cyclosporine are useful differently. Steroid-resistant NS management is difficult; most patients show progressive renal damage and cannot achieve remission.

5.1. Idiopathic NS in children

Calcineurin inhibitors such as cyclosporine, tacrolimus induces remission in a particular percentage of patients, but side effects involves nephrotoxicity. Reduction of proteinuria is also possible in children using angiotensin converting enzyme inhibitors. Steroid dependence and resistance, trials are necessary[20].

It covers more than 90% cases between 1-6 years of age[21]. It is defined by the association of the clinical features of NS with renal biopsy findings of diffuse foot process effacement on electron microscopy and minimal change on light microscopy[22]. Histologic findings of MCD are found in most patients, such vast majority of patients with MCD respond to glucocorticoid therapy[23].

5.2. Idiopathic NS in adults

The association of spontaneous bacterial peritonitis with NS is common in children, but it is extremely rare in adults. Only 14 cases have been reported in the literature. Research showed two adult cases who developed spontaneous bacterial peritonitis during a course of NS, and described the clinical findings. Both patients had renal failure at admission and had a diagnosis of NS due to amyloidosis before the development of peritonitis. The causative agent could not be isolated from ascitic fluid culture in either patient[24].

Spontaneous bacterial peritonitis is a infection caused by bacteria and is of ascitic fluid, which occurs in the absence of any other source of intra-abdominal infection. It is a common complication of childhood NS, and is rare in adults with NS[25] (Table 2).

6. Precaution

6.1. Management

Normal diet was required including normal protein intake, salt restriction during relapses, limited oily foods and no junk foods and avoiding sauces with salt *etc*. Considering the antibiotics, oral penicillin was used during relapses to defense against pneumococcus causing infection. Use of frusemide if fluid restriction and salt restriction alone not effective in controlling oedema formation. IV albumin was used in severe oedema only, and maximum dose 1g/kg of 20% albumin over minimum for 4 h. Steroid therapy was applied when diagnosis was proved. If there is possibility of secondary NS discussion with nephrologist, it should be done prior to commencing steroid therapy[31].

6.2. Role of immunity

Idiopathic NS is thought to be the result of an immunological dysfunction, which brings a circulating factor thus permeability of the glomerular filtration barrier is modified. In 1974, Shalhoub[32] proposed that minimal change nephritic syndrome was a disorder of lymphocyte function, thus increased plasma levels of a lymphocyte-derived permeability factor. For example, the response to immunosuppressive drugs and the association with Hodgkin disease and allergy. Allergy plays a role as reviewed by van den Berg and Weening[33]. Many reports showed that some patients developed NS after having experienced allergic reactions to inhaled allergens, with vaccinations, food and insect stings. The incidence of atopy was reportedly higher in patients with idiopathic NS than in healthy subjects, ranging from 17% to 40% in minimal change nephritic syndrome patients compared with 10%-23% in age-matched control subjects. Elevated production of immunoglobulin E by B-lymphocytes occurred in case of allergy, and several researchers had reported an elevation of immunoglobulin E in the serum of NS patients.

The role of circulating factor is particularly suggested by the following observations[34].

1) proteinuria after transplantation;

2) proteinuria passed to foetus;

3) after injection of serum proteinuria transferred to rat

As immunity enhancers homoeopathy medication can also be given side by side.

6.3. Herbal approach in management of NS

6.3.1. Guduchi [Tinospora cordifolia (T. Cordifolia)]

Swiss albino mice was used as an animal model, and urotoxicity was studied after inducing acute dose of cyclophosphamide. An alcoholic extract of the plant *T. Cordifolia* was administered (200 mg/kg *i.p.*) for 5 d for reduced cyclophosphamide (CP) (1.5 mmol/kg body weight *i.p.*) induced urotoxicity. Morphological analysis of bladder, and also decreased urea nitrogen level in

blood as well as protein in urine were evidence for reduced CP induced urotoxicity. Severe necrotic damage was reported by Histopathological analysis of the bladder of CP alone treated group whereas normal bladder was reported in *T. cordifolia* treated group.

The study showed uroprotective role of *T. cordifolia* from CP induced toxicities[35].

6.3.2. Ashwagandha [Withania somnifera (W. somnifera)]

Rat was used as an animal model. Doses 250, 500 and 750 mg/kg of *W. somnifera* root extract were administered orally to rats for 14 d before gentamicin induced nephrotoxicity (GEN) treatment and thereafter concurrently with GEN (100 mg/kg) for 8 d. In GEN-treated rats, all factors such as kidney weight, urea, creatinine, urinary protein and glucose increased, body weights and potassium reduced, which was histopathologically confirmed by tubular necrosis. However, *W. somnifera* (500 mg/kg) significantly reversed these changes when compared to other two doses of *W. somnifera* (250 and 750 mg/kg), and no significant changes in the levels of sodium in the experimental animals compared to control. Results showed the nephroprotective effects of *W. somnifera*, which could be by enhancing antioxidant activity with natural antioxidants and scavenging the free radicals[36].

6.3.3. Haridra (Curcuma longa)

The nephroprotective and diuretic effects of *Petroselinum sativum*, *Eruca sativa* and *Curcuma longa*, alone and in combination were investigated against gentamicin (GM)- induced nephrotoxicity. Animal model used was male Sprague Dawley rats. Forty two animals were randomly distributed into 6 equal groups. Rats in the first group were injected intra-peritoneally (*i.p.*) with saline solution (0.2 mL). Second group was injected with GM (80 mg/kg body weight) for 8 consecutive days. The other four groups were given orally aqueous infusion of the three herbs, alone and combined, (1 mL/rat, 150 mg/kg body weight) along with GM.

Blood and urine samples were taken for biochemical analysis after 24 h of the last administration. For detecting oxidant/antioxidant parameters and for histopathology, kidney specimens were taken. The results showed that GM-induced nephrotoxicity characterized by renal dysfunction as evident by biochemical and histopathological alterations, elevated lipid per-oxidation and reduced activity of antioxidant enzymes in kidney tissues was ameloriated by oral administration of aqueous infusion of *Petroselinum sativum*, *Eruca sativa* and *Curcuma longa* herbs. It caused a nephroprotective effect evident by significant decreases in the elevated serum urea, creatinine and alkaline phosphatase activity and normalized the serum electrolytes level of sodium and potassium. It increased urine output and urinary concentration of Na^+ and K^+, denoting a diuretic activity. The nephroprotective effect of herbs could be due to the antioxidant effect of these herbs as evident by increasing activity of antioxidant enzymes. Thus, mixture of these three herbs are beneficial for patients having renal diseases[37].

7. Treatments

Results of NS as acute renal failure, edema, hypercoagulation, and infections should be treated and dealed properly. Immunosuppressive drugs can be used to prevent relapses. However, recent experiments have shown that steroids and cyclosporine, may also act directly on the podocyte to stabilize its structure[38,39].

8. Conclusion

Major advances in the pathophysiological understanding have led to new treatment strategies in the past several years, even though the occurrence of primary causes of NS is low. Therefore, clinical trials should be done, and adult patients with NS should be treated with clinical trials in the future. Many new treatment targets identified by basic science have been proposed. More study of these new targets and those identified in the future will potentially lead to novel advances in the treatment of NS, with higher effectiveness in reducing proteinuria.

Conflict of interest statement

The authors declare that they have no conflict of interest.

References

[1] Bagga A, Ali U, Banerjee S, Kanitkar M, Phadke KD, Senguttuvan P, et al. Management of steroid sensitive nephrotic syndrome: Revised guidelines. *Indian Pediatr* 2008; **45**(3): 203-214.

[2] Hendrickse RG, Adeniyi A. Quartan malarial nephrotic syndrome in children. *Kidney Int* 1979; **16**(1): 64-74.

[3] Morel-Maroger L, Saimot AG, Sloper JC, Adam C, Niang I, Payet M. Tropical nephropathy and tropical extra-membraneous glomerulo-nephritis of unknown etiology in Senegal. *Br Med J* 1975; **1**: 541-546.

[4] Allison AC, Hendrickse RG, Edington GM, Houba V, De Petris S, Adeniyi A. Immune complexes in the nephrotic syndrome of African children. *Lancet* 1969; **1**: 1232-1238.

[5] Houba V, Lambert PH, Voller A, Soyanwo MA. Clinical and experimental investigation of immune complexes in malaria. *Clin Immunol Immunopathol* 1976; **6**(1): 1-12.

[6] Lennon RL, Massengill SF, Yao L. Nephroti syndrome in children. *Lancet* 2010; **362**: 36-42.

[7] Gipson DS, Massengill SF, Yao L, Nagaraj S, Smoyer WE, Mahan JD, et al. Management of childhood onset nephrotic syndrome. *Pediatrics*

2009; **124**(2): 747-757.

[8] Arant BS Jr, Singer SA, Bernstein J. Steroid-dependent nephrotic syndrome. *J Pediatr* 1982; **100**(2): 382-333.

[9] Gulati S, Kher V, Elhence R, Kumar P, Sharma RK, Gupta A. Treatment of nephrotic syndrome. *Ind Pediatr* 1994; **31**(2): 165-170.

[10]Haas ME, Levenson AE, Sun X, Liao WH, Rutkowski JM, de Ferranti SD, et al. The role of proprotein convertase subtilisin/kexin type 9 in nephrotic syndrome-associated hypercholesterolemia. *Circulation* 2016; **134**(1): 61-72.

[11]Singhal R, Brimble KS. Thromboembolic complications in the nephrotic syndrome: Pathophysiology and clinical management. *Thromb Res* 2006; **118**(3): 397-407.

[12]Caridi G, Perfumo F, Ghiggeri GM. NPHS2 (Podocin) mutations in nephrotic syndrome. Clinical spectrum and fine mechanisms. *Pediatr Res* 2005; **57**(5 Pt 2): 54R-61R.

[13]Moulin P, Appel GB, Ginsberg HN, Tall AR. Increased concentration of plasma cholesteryl ester transfer protein in nephrotic syndrome: Role in dyslipidemia. *J Lipid Res* 1992; **33**(12): 1817-1822.

[14]Lewis MG, Loughridge LW, Phillips TM. Immunological studies in nephrotic syndrome associated with extrarenal malignant disease. *Lancet* 1971; **2**(7716): 134-135.

[15]Hinkes B, Wiggins RC, Gbadegesin R, Vlangos CN, Seelow D, Nürnberg G, et al. Positional cloning uncovers mutations in PLCE1 responsible for a nephrotic syndrome variant that may be reversible. *Nat Genet* 2006; **38**(12): 1397-1405.

[16]Vernier RL, Klein DJ, Sisson SP, Mahan JD, Oegema TR, Brown DM. Heparan sulfate-rich anionic sites in the human glomerular basement membrane. Decreased concentration in congenital nephrotic syndrome. *N Engl J Med* 1983; **309**(17): 1001-1009.

[17]Joven J, Villabona C, Vilella E, Masana L, Albertí R, Vallés M. Abnormalities of lipoprotein metabolism in patients with the nephrotic syndrome. *N Engl J Med* 1990; **323**(9): 579-584.

[18]McCarthy HJ, Bierzynska A, Wherlock M, Ognjanovic M, Kerecuk L, Hegde S, et al. Simultaneous sequencing of 24 genes associated with steroid-resistant nephrotic syndrome. *Clin J Am Soc Nephrol* 2013; **8**(4): 637-648.

[19]Drewe E, McDermott EM, Powell RJ. Treatment of the nephrotic syndrome with etanercept in patients with the tumor necrosis factor receptor–associated periodic syndrome. *N Engl J Med* 2000; **343**(14): 1044-1045

[20]Bagga A, Mukta M. Nephrotic syndrome in children. *India J Med Res* 2005; **122**: 13-28.

[21]Habib R, Kleinknecht C. The primary nephrotic syndrome of childhood: Classification and clinicopathologic study of 406 cases, in Pathology Annual. In: Sommers SC, editor. New York: Appleton-Century-Crofts; 1971.

[22]White RH, Glasgow EF, Mills RJ. Clinicopathological study of nephrotic syndrome in childhood. *Lancet* 1970; **1**(7661): 1353-1359.

[23]Research Support, Non-U.S. Gov't. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the international study of kidney disease in children. *J Pediatr* 1981; **98**(4): 561-564.

[24]Chuang TF, Kao SC, Tsai CJ, Lee CC, Chen KS. Spontaneous bacterial peritonitis as the presenting features in an adult with nephrotic syndrome. *Nephrol Dial Transpl* 1999; **14**: 181-182.

[25]Chen MC, Lam KK, Hsu KT. Spontaneous bacterial peritonitis in adult patients with primary nephrotic syndrome. *Changgeng Yi Xue Za Zhi* 1999; **22**(2): 227-233.

[26]Lilova MI, Velkovski IG, Topalov IB. Thromboembolic complications in children with nephrotic syndrome in Bulgaria (1974-1996). *Pediatr Nephrol* 2000; **15**(1-2): 74-78

[27]Hamed RM, Shomaf M. Congenital nephrotic syndrome: A clinico-pathologic study of thirty children. *J Nephrol* 2001; **14**(2): 104-109.

[28]Kerlin BA, Blatt NB, Fuh B, Zhao S, Lehman A, Blanchong C, et al. Epidemiology and risk factors for thromboembolic complications of childhood nephrotic syndrome: A Midwest Pediatric Nephrology Consortium (MWPNC) study. *J Pediatr* 2009; **155**(1): 105-110.

[29]Cherng SC, HuangWS, Wang YF, Yang SP, Lin YF. The role of lung scintigraphy in the diagnosis of nephrotic syndrome with pulmonary embolism. *Clin Nucl Med* 2000; **25**(3): 167-172.

[30]Wysokinski WE, Gosk-Bierska I, Greene EL, Grill D, Wiste H, McBane RD 2nd. Clinical characteristics and long-term followup of patients with renal vein thrombosis. *Am J Kidney Dis* 2008; **51**(2): 224–232.

[31]Wong W, Prestidge C. Nephrotic syndrome in childhood. *Starship Children's Health Clin Guid* 2013: 1-5.

[32]Shalhoub RJ. Pathogenesis of lipoid nephrosis: A disorder of T cell function. *Lancet* 1974; **2**(7880): 556-560.

[33]Van den Berg JG, Weening JJ. Role of the immune system in the pathogenesis of idiopathic nephrotic syndrome. *Clin Sci* 2004; **107**(2): 125-136.

[34]McCarthy ET, Sharma M, Savin VJ. Circulating permeability factors in idiopathic nephrotic syndrome and focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol* 2010; **5**(11): 2115-2121.

[35]Hamsa TP, Kuttan G. Tinospora cordifolia ameliorates urotoxic effect of cyclophosphamide by modulating GSH and cytokine levels. *Exp Toxicol Pathol* 2012; **64**(4): 307-314.

[36]Singh RG, Singh P, Singh PK, Usha, Agrawal A, Upadhyay BN, et al. Immunomodulating and antiproteinuric Effect of Hippophae rhamnoides (Badriphal) in idiopathic nephrotic syndrome. *J Assoc Physicians India* 2013; **61**(6): 397-399.

[37]Pathak NN, Rajurkar SR, Tarekh S, Badgire VV. Nephroprotective effects of carvedilol and Curcuma longa against cisplatin-induced nephrotoxicity in rats. *Asian J Med Sci* 2014; **5**(2): 91-98.

[38]Faul C, Donnelly M, Merscher-Gomez S, Chang YH, Franz S, Delfgaauw J, et al. The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. *Nat Med* 2008; **14**(9): 931-938.

[39]Xing CY, Saleem MA, Coward RJ, Ni L, Witherden IR, Mathieson PW. Direct effects of dexamethasone onhuman podocytes. *Kidney Int* 2006; **70**(6): 1038-1045.